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EXAMINER	
CHANDRA, GYAN	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 02/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,623	ERIKSSON ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,17,22,23 and 27-29* is/are pending in the application.

4a) Of the above claim(s) *22 and 27-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/18/02,9/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group 1, claims 1-14, 17, 23 and 27-29 in the reply filed on 10/12/2004, and a polynucleotide sequence encoding the amino acid sequence of SEQ ID NO: 6 in the reply filed on 12/21/2004 is acknowledged. The traversal is on the ground(s) that all five polynucleotide sequences 4, 6, 8, 36 and 38 are closely related and have substantial common structure and function. This is not found persuasive because SEQ ID NO: 4 is 96.8% identical to SEQ ID NO: 8; SEQ ID NO: 36 is 85% identical to SEQ ID NO: 8; SEQ ID NO: 38 is a result of 6 amino acid deletion of SEQ ID NO: 36. These sequences have substantial differences and that each polynucleotide sequence could function differently and independent from each other. Searching polynucleotide sequences with 96.8 % or 85% identity encompasses numerous possibilities for mutations, insertions and deletions along the length of a polypeptide. Therefore, this creates an undue burden on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claim 22 belongs to Group 11 as set forth in Restriction/Election sent on 08/09/204.

Claims 27-29 are drawn to non elected polynucleotide sequence encoding polypeptide of SEQ ID NO: 36, 38 or 40. The restriction requirement mailed on 09/09/2004 identified groups 1-5 as a polynucleotide sequence encoding the

polypeptide of SEQ ID NOs: 4,6, 8, 36 or 38. However, the restriction requirement missed to include a polynucleotide encoding SEQ ID NO: 40, which also needed a sequence election.

Claims 15-16, 18-21, and 24-26 are canceled.

Claims 1-14,17, and 23 are examined on the merits to the extent that they read on the elected polynucleotide sequence encoding the polypeptide of amino acid sequence of SEQ ID NO: 6.

Information Disclosure Statement

The information disclosure statement filed 09/23/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Miyama et. al. and Voet et. al. citations are not submitted with the instant application.

Claim Objections

Claims 1, 4, and 23 are objected to as reciting non-elected sequences. Amendment of the claims to delete the nonelected subject matter is requested.

Claims 5-7 are objected to because of the following informalities: claims 5,6, and 7 have typographical error in " nucleic acid molecular". The examiner interprets " nucleic

acid molecular" as " nucleic acid molecule" for the examination purpose only.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14, 17, and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a polynucleotide having at least 85%, 90 % or 95% identity with the polypeptide of amino acid SEQ ID NO: 6 and hybridization to one of claimed sequences. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or any other disclosed distinguished feature. Thus the claims are drawn to a genus of nucleic acids that is defined solely by sequence identity or hybridization ability.

To provide undisclosed possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics for the genus. The factors to

be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the chemical product, or any combination thereof. There is not even identification of any particular portion of the structure that must be conserved. Further, the recited activity is not specific because specification discloses that the PDGF-D activity is defined as " the ability to stimulate or enhance, or both of proliferation, differentiation, growth and motility of a cell expressing a PDGF-D receptor". These biological activities are very broad. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is *whatever is now claimed* (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the* University of California v. Eli Lilly & Co., 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the* University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states an adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention.

As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolating it. The compound itself is required. See Fiers v.Revel, 25USPQ2d 1601 at 1606 (CAFC 1993) and Amgen v.Baird, 30 Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 148 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for

that broad class. The specification provides only the bovine sequence. Therefore, only the isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 6, but not the breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claims 1-14, 17, and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)).

Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

Claims 1-14, 17, and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of amino acid sequence of SEQ ID NO: 6, does not reasonably provide enablement for biologically active protein with either 85%, 90 % or 95% identity to amino acid sequence of SEQ ID NO: 6 or hybridization under stringent conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the invention commensurate in scope with these claims.

The Nature of Invention: The claimed invention is drawn to polynucleotide

encoding a polypeptide having the amino acid sequence set forth in SEQ ID NO: 6 or a polypeptide having an amino acid sequence at least 85%, 90 % or 95% identical to the amino acid sequence given in SEQ ID NO: 6.

The state of the prior art and the predictability or lack thereof in the art: The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinants to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitution (see Bowie et.al., 1990, Science 247: 1306-1310, page. 1306, column 2, paragraph 2; Wells, 1990, Biochemistry 29:8509-8517)

The amount of direction or guidance present and the presence or absence of working examples: Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g., by amino acid substations or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening a protein with 85%, 90 % or 95% identity, it is merely an invitation to the artisan to use the invention as a starting point for further experimentation. Even if a protein with either 85%, 90 % or 95% homology were

identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that a functional protein which is either 85%, 90 % or 95% homologous to the SEQ ID NO: 6, must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy function of the protein. Therefore a large number of experimentation would be required to obtain a functional protein either with 85%, 90 % or 95% identity with SEQ ID NO: 6. Furthermore, once a protein is obtained with 85%, 90 % or 95% identity with SEQ ID NO: 6, it would require to huge experimentation to evaluate its functionality.

The breadth of the claims and the quantity of experimentation needed: Due to the large quantity of experimentation necessary to generate the indefinite number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of invention, the state of prior art which establishes unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 10-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated or cultured cell comprising an expression vector, does not reasonably provide enablement for a host cell comprising

an expression vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Examiner has interpreted the claim as reading on isolated host cells, as well as host cells in the context of a multicellular, transgenic organism and host cells intended for gene therapy. The specification of the instant application teaches that a protein encoded by gene of SEQ ID NO: 6 can be expressed in transgenic animals and any technique known in the art may be used to introduce the transgene into animals to produce the founder lines of transgenic animals (section, Cellular transfection and Gene therapy page 26, paragraph 52). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated PDGF-D gene of SEQ ID NO: 6 is demonstrated to express the PDGF-D peptide. There are also no methods or working examples in the specification indicating that a multicellular animal has PDGF-D "knocked out". The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Additionally, for example, the specification discloses that a number of vector can be used to introduce a PDGF-D transgene include non-viral delivery of nucleic acid and DNA or RNA based viral delivery for gene therapy. However, the literature teaches that the production of transgenic animals by microinjection of embryos suffers from a

number of limitations, such as the extremely low frequency of integration events and the random integration of the transgene into the genome which may disrupt or interfere with critical endogenous gene expression (Wigley et al. Reprod Fert Dev 6: 585-588, 1994). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems, as homologous recombination events are even rarer than random events. Therefore, in view of the extremely low frequency of both targeted and non-targeted homologous recombination events in microinjected embryos, it would have required undue experimentation for the skilled artisan to have made any and all transgenic non-human animals according to the instant invention. Furthermore, regarding gene targeting in embryonic stem cells, the specification does not provide guidance for identifying and isolating embryonic stem cells or for identifying other embryonal cells which are capable of contributing to the germline of any animal. At the time of filing, Campbell et al. teaches that, "in species other than the mouse the isolation of ES cells has proved more difficult. There are reports of ES-like cell lines in a number of species...However, as yet there are not reports of any cell lines which contribute to the germ line in any species other than mouse" (Campbell et al. Theriogenology 47(1): 63-72, 1997; see pg 65, 2nd paragraph). Thus, based on the art recognized unpredictability of isolating and using embryonic stem cells or other embryonal cells from animals other than mice to produce transgenic animals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells which can contribute to the germ line of any non-human mammal other than the mouse, such as dogs or cows, the skilled artisan

would not have had a reasonable expectation of success in generating any and all non-human transgenic animals using ES cell technology.

The specification also discloses that "nucleotide constructs encoding such PDGF-D protein can be used to genetically engineer host cells to express such products in vivo" and that these products can be used in gene therapy approaches for the modulation of PDGF-D expression. However, the specification does not teach any methods or working examples that indicate a PDGF-D nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the PDGF-D nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce

and express a PDGF-D nucleic acid into the cell of an organism. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express a PDGF-D nucleic acid in the cell of an organism or be able to produce a PDGF-D protein in that cell.

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the PDGF-D protein and to introduce and express a PDGF-D nucleic acid in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce a PDGF-D nucleic acid in the cell of an organism to be able produce that PDGF-D, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. (This rejection could be overcome by amending the claims to recite, for example, "An isolated host cell...").

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14, 17, and 23, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, the phrase "stringent conditions" renders the claim indefinite

because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. The limitation "stringent conditions" is conditional and the defining conditions are not recited in the claim or the specification. See MPEP § 2173.05(d).

Claim 14 is vague and indefinite in reciting "....RKSK or structurally conserved amino acid sequence thereof" because it is unclear what other structurally conserved amino acid sequences can replace "RKSK" at the proteolytic site.

Conclusion

No claims are allowed.

The polynucleotide sequence encoding polypeptide of SEQ ID NO: 6 is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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AU 1646
14 January 2005

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